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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/894,246	05/22/1998	MICHEL PERRICAUDET	EX95001-US	8790

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WILEY, REIN & FIELDING, LLP
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WASHINGTON, DC 20006

EXAMINER

CHEN, SHIN LIN 29

ART UNIT PAPER NUMBER

1632

DATE MAILED: 03/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No. 08/894,246	Applicant(s) Perricaudet et al.
Examiner Shin-Lin Chen	Art Unit 1632



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on Feb 6, 2003
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 65-108 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 65-108 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). _____
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) Other: _____

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DETAILED ACTION

Applicants' amendment filed 2-6-03 has been entered. Claims 66 and 85 have been amended. Claims 65-108 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 66, 67, 85 and 86 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant's arguments filed 2-6-03 have been fully considered but they are not persuasive.

Applicants amended claims 66 and 86 to read on "selected from cyclosporin..., or a monoclonal antibody or polyclonal antibody that...". It is unclear whether the group to be selected from comprises a monoclonal antibody or a polyclonal antibody or both. Changing the claims to read on "selected from **the group consisting of** cyclosporin..., a monoclonal antibody, **and** a polyclonal antibody that..." would be remedial.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 82, 88 and 107 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and is repeated for the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26). Applicant's arguments filed 2-6-03 have been fully considered but they are not persuasive.

Applicants argue that naturally occurring strains of adenovirus that include different gp19 sequences have been pointed out and genes with similar functional properties can be obtained by any technique known to one skilled in the art. Applicants further cite lines 15-20 on page 18 of the specification that states "other genes which are homologous or which have similar functional properties...can be obtained by any technique which is known to the person skilled in the art..." (Amendment, p. 4, 5). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26). As discussed in the preceding Official action mailed 8-6-02 (Paper No. 26), the specification only discloses site-directed mutagenesis in general but fails to provide sufficient description for a sequence that contains one or more point mutations compared to a wild type human Ad5 sequence and encodes a mutated gp19k protein having immunosuppressive activity as wild type gp19k protein or how to use the site-directed mutagenesis method to obtain said sequence encoding mutated gp19k protein that still retain

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immunosuppressive activity. There is no nexus between the stated general site-directed mutagenesis method and the claimed sequence coding for an adenoviral gp19 protein containing one or more point mutations, which would encompass numerous different point mutations of gp19 sequence. The specification also fails to disclose the structural feature that contributes to immunosuppressive activity of gp19k protein and which amino acid residue(s) can be removed but the resulting mutated protein still retain the immunosuppressive activity of gp19k protein. Further, other genes that are homologous to gp19 gene or encode proteins having similar function as gp19 protein are different from mutated gp19 gene because a mutated gp19 gene has mutations within the nucleotide sequence of the known gp19 gene but a homologous gene to gp19 gene is a gene, which encodes a protein that **might** have similar function as gp19 protein, isolated from other species. Thus, the specification fails to provide support for "a sequence coding for an adenoviral gp19k protein that contains one or more point mutations compared to wild type human Ad5 adenovirus sequence, and the gp19k protein retains an immunosuppressive activity" and it is considered a new matter.

Applicants cite Flomenberg et al. and Hermiston et al. references and argue that those references show different gp19 sequences at N-terminal and mutations in the adenoviral gp19k sequence can be made by one skilled in the art (amendment, p. 5, 6). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26) and the reasons set forth above. Those gp19k sequences cited in the references are gp19k sequences derived from different adenovirus species. They are homologous gp19k genes

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but they are not mutated human Ad 5 gp19 gene sequences. Further, the specification fails to disclose the structural feature that contributes to immunosuppressive activity of gp19k protein and one skilled in the art at the time of the invention would not know which amino acid residue(s) can be removed but the resulting mutated protein still retain the immunosuppressive activity of gp19k protein.

Applicants argue that the specification teaches how to use the gp19k protein in the methods and compositions of the invention and an assay to test the immunosuppressive activity of the adenoviral vector. Applicants further argue that one skilled in the art know of gp19 sequence variations (amendment, p. 6). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26) and the reasons set forth above.

5. Claims 102-108 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and is repeated for the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26). Applicant's arguments filed 2-6-03 have been fully considered but they are not persuasive.

Applicants argue that the "sequence of interest" is not particularly relevant concern for the production and use of the vector and one skilled in the art would be able to identify any effect

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of the expressed gene of interest through assays and methods given in the specification (amendment, p. 7). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26). The claims read on a method of prolonging the survival of a cell expressing a sequence of interest by introducing an adenovirus expressing said sequence of interest and **the expression of the sequence of interest results in prolonged cell survival**. Thus, to the contrary of applicants' argument, **the expression of the sequence of interest** is an essential part of the claimed invention and is very much relevant to the use of the vector for prolonging cell survival *in vitro* or *in vivo*. The claims encompass any sequence of interest that encodes any protein, ribozyme and any antisense RNA. However, the specification fails to provide adequate guidance and evidence that expression of any of the sequence of interest encoding any protein, such as p53, aFGF, bFGF, factor VII, or factor IX, any ribozyme, or antisense RNA could result in prolonged cell survival *in vitro* or *in vivo*.

Applicants argue that example 2.3 shows prolonged expression of a sequence of interest, i.e. beta-gal, and there is no requirement that the "sequence of interest" provide some activity to prolong expression (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26) and the reasons set forth above.

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6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 65-81, 83-87 and 89-101 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leibowitz et al., 1994 (N) in view of Linsley et al., 1992 (U) and Nabel et al., 1994 (Annals New York Academy of Sciences, Vol. 714, p. 247-252) and is repeated for the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26). Applicant's arguments filed 2-6-03 have been fully considered but they are not persuasive.

Applicants argue the rejection improperly uses a hindsight analysis to reconstruct the claimed invention and that Linsley discusses the CTLA4g molecule but does not mention an adenovirus, and neither Nabel nor Leibowitz provide motivation to combine an adenoviral vector

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with an immunosuppressive agent (amendment, p. 9). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Leibowitz teaches construction of a recombinant Ad5 adenovirus vector expressing adenoviral E19 (i.e. gp19K) and the expressed gp19k protein can reduce transplant rejection by the recipient organism's immune system. Leibowitz also teaches using adenoviral vector to introduce E19 coding sequence into donor cells *in vitro* or *in vivo* to reduce transplant rejection by the recipient organism on the donor cells (e.g. p. 10). Linsley shows CTLA4Ig treatment *in*

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vivo suppresses T-cell dependent antibody responses to sheep erythrocytes and large doses of CTLA4Ig suppresses response to a second immunization. Nabel teaches using recombinant adenoviral vector expressing FGF-1 for gene transfer into vascular cells and discloses the problem of host immune response to the adenoviral vector for gene transfer. It was well known in the art to use immunosuppressive agent to reduce transplant rejection by recipient organism. Since Nabel points out the problem of host immune response to the adenoviral vector for gene transfer, one of ordinary skill at the time of the invention would have been motivated to combine immunosuppressive agent, such as CTLA4Ig, as taught by Linsley with the adenoviral vector as taught by Leibowitz.

Applicants indicate confusion on page 8-9 of Official action and argue that there is no relevance of the MHC class I issue to adenoviral vector and Nabel does not offer a suggestion for resolving the “gene persistence” issue (amendment, p. 10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26) and the reasons set forth above. Examiner is unclear about the “gene persistence” issue mentioned by applicants. The teachings of Leibowitz, Linsley and Nabel are as discussed above in the preceding paragraph and preceding Official action mailed 8-6-02. The main teaching by Leibowitz is that the expressed gp19k protein can reduce transplant rejection by the recipient organism’s immune system. Nabel discloses the problem of host immune response to the adenoviral vector for gene transfer. It was well known in the art to use immunosuppressive agent to reduce transplant rejection by recipient organism. Since Nabel points out the problem of host

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immune response to the adenoviral vector for gene transfer, one of ordinary skill at the time of the invention would have been motivated to combine immunosuppressive agent, such as CTLA4Ig, as taught by Linsley with the adenoviral vector as taught by Leibowitz. Thus, there is motivation to combine the teachings of Leibowitz, Linsley and Nabel in the knowledge generally available to one of ordinary skill in the art.

Applicants argue that no objective teachings suggests combining an immunosuppressive agent with an adenoviral vector or an adenoviral vector comprising a gp19k sequence and it is only with improper hindsight to arrive at claimed invention from the cited references (amendment, p. 11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26) and the reasons set forth above.

Applicants argue that the specification discloses unexpected results in prolonging expression period from the claimed invention (amendment, p. 11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-6-02 (Paper No. 26) and the reasons set forth above. Claims 65-81 are composition claims that comprises a recombinant adenovirus and an immunosuppressive agent and claims 83-87 and 89-101 are directed to a method of expressing a sequence of interest from an adenovirus. The claims do not specify any unexpected prolonged expression of any gene. Nowhere in the claims the prolonging expression of any gene is mentioned. Thus, the unexpected results in prolonging expression is irrelevant to the claims in dispute.

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Conclusion

No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

A handwritten signature in black ink, appearing to read "Schen".